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REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 54-71 are pending in the present application. Support for claims 54-71 may be found in original claims 1-25 and generally throughout the specification. In particular, the Examiner's attention is directed to page 7, lines 13-18; and page 16, lines 20-30. Claims 1-54 have been canceled.

In the outstanding Official Action, claims 1-25 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants believe the present amendment obviates this rejection.

In imposing the rejection, claims 1 and 21 were rejected for containing the phrase "since the initial culture thereof". The Official Action alleged that this phrase was indefinite. However, as noted above, claims 1-54 have been canceled. New claims 54-71 have been drafted in a manner so that this phrase no longer appears in the claims.

Claim 2 was rejected because it was allegedly unclear what differentiated the method of claim 2 from the method of claim 1. Claims 1 and 2 have been cancelled. Claim 54 recites a process for deriving dendritic cells from mononuclear cells in

culture within 3 days wherein said mononuclear cells are peripheral blood mononuclear cells (PBMC) or CD14+ monocytes. As a result, applicants believe that it is clear to one skilled in the art that the claimed process results in the dendritic cells of the present invention within 3 days.

Claims 3 and 4 were rejected for reciting the term "any synthetic type I IFN". However, the Examiner's attention is respectfully directed to the present application at page 6, lines 1-10, wherein this phrase is given meaning. Moreover, as evidence that this phrase is definite to one skilled in the art, the Examiner's attention is directed to the publication: Alton, K., Y. Stabinsky, R. Richards, B. Ferguson, L. Goldstein, B. Altrock, L. Miller and N. Stebbings. 1983. *Production, characterization and biological effects of recombinant DNA derived human IFN-a and IFN-y analogs*. This phrase is also referred to in "The Biology of the Interferon System" (E. De Maeyer and H. Schellenkens, pp. 119-128. Elsevier, Amsterdam). A person skilled in the art would understand that this phrase includes any synthetic type I IFN produced from recombinant DNA, including in particular synthetic consensus IFN (CIFN) whose sequence is based on a consensus derived from amino acid sequences of human IFN-alpha. Therefore, applicants believe consider that this expression is definite to a person skilled in the art.

Claims 5 and 12 were rejected for reciting the phrase "final concentration". The Official Action alleged that the scope of "final concentration" was unclear. In the interest of advancing prosecution, the claims have been drafted in a manner so that this phrase is no longer recited. As a result, applicants believe that the new claims obviate this rejection.

Claims 13-14 and 22 were vague and indefinite as they recited a method employing a "cell growth factor". The Official Action alleged that this recitation was indefinite. In drafting the new claims, the term "cell growth factor" has been replaced by "growth factor which promotes monocyte/dendritic cell survival in culture". Thus, the term growth factor is further defined in the claims. In view of this change, applicants believe that the claims are definite to one of ordinary skill in the art.

The outstanding Official Action also rejected claims 19-20 for reciting the phrase "maturation agent". However, applicant submits that a person skilled in the art of *ex vivo* preparation of dendritic cells would know what kind of agent to employ and at what concentration levels to administer the maturation agent. Annexed are two publications from CELLA et al. for illustration. Also, the specification discloses on page 4 that, after differentiation of dendritic cells from monocytes "further dendritic cell [DENDRITIC CELL] maturation can be driven by the addition of TNF-alpha, IL-1, LPS, monocyte-conditioned medium or sCD40L".

Thus, in view of the above, applicants believe that the term "maturation agent" is definite to one skilled in the art.

The Official Action rejected claim 22 for reciting the term "which can be". However, new claims 54-71 have been drafted in a manner so that this term is no longer recited in the claims.

Claims 17-18 were vague and indefinite because they recited the term "250-1000 U/ml". In the new claims, this informality has been corrected and the expression "250-1000 U/ml" has been replaced by the term "250-1000 IU/ml". In view of the above, applicants believe that this rejection has been obviated.

In the outstanding Official Action, claims 1-25 were rejected under 35 USC §112, first paragraph, as allegedly being based on a disclosure which is not enabling. This rejection is respectfully traversed.

In imposing the rejection, the Official Action contends that only cultures employing 1000 IU/ml IFN resulted in functional dendritic cells. The Official Action also alleged that the addition of 500 IU/ml GM-CSF was essential to the practice of the claimed invention.

However, as the Examiner is aware, the present application discloses an invention related to a process for generating dendritic cells from mononuclear cells in culture, wherein said mononuclear cells are put in contact with type I IFN. The present application provides several comparative

experiments, wherein different types of IFN-alpha are tested in different concentration levels.

Applicants believe that by reading the specification, a person skilled in the art would understand and practice the claimed invention, without undue experimentation by using any concentration of type I IFN greater than 100 IU/ml. Indeed, while the specification provides one example wherein the use of 100 IU/ml of IFN does not result in the claimed method, applicants note that the claimed invention recited that the IFN was a concentration "greater than" IU/ml.

Nevertheless, in the interest of advancing prosecution, independent claims 54 and 63 have been drafted to recite that IFN is at a concentration "greater than 400 IU/ml". As to independent claims 68 and 69, claims 68 and 69 recite that the type I IFN is at a final concentration of 400-10,000 IU/ml. Claims 68 and 69 further recite that GM-CSF in a concentration of 250-1,000 IU/ml.

The Examiner is respectfully reminded that a specification containing a description of a claimed invention is presumed enabling, unless there is reason to doubt the objective truth thereof. Indeed, it is a well founded principle that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. As stated by the Court of Customs and Patent Appeals

in the case of *In re Dinh-Nguyen and Stanhagen,* 181 USPQ 46 (CCPA 1974):

> Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. 181 USPQ at 47.

Such a standard must be applied with great care when the conjecture by the Patent Office is contrary to the teachings of the specification. When reviewing the Office Action on this point, it is apparent that no evidence is adduced that is in any way inconsistent with the teaching of the specification. The Official Action does not present any evidence as to why the claimed ranges of IFN and GM-CSF would not result in the dendritic cells of the present invention.

Thus, in view of the above, applicants believe that the claimed invention is enabled by the present disclosure.

Claims 1-25 were rejected under 35 USC 102(b) as allegedly being anticipated by BARTHOLOME et al. This rejection is respectfully traversed.

BARTHOLOME et al. examine the effect of IFN-beta on the differentiation of monocytes into dendritic cells by a conventional GM-CSF/IL-4 treatment in 6-7 days. BARTHOLOME et al. observe that cells obtained in the presence of either GM-CSF and IL-4 or GM-CSF, IL-4 and IFN-beta displayed the morphology of immature dendritic cells (page 472, right column and page 473, right column), with a phenotype of immature dendritic cells (high

level of HLA-DR, CD86 and CD80, absence of CD83). BARTHOLOME et al. observe (page 475) that the ability of IFN-beta treated dendritic cells to induce proliferation of allogeneic T cells is not superior to that of untreated dendritic cells, and conclude that type I IFN may have differential effects on dendritic cells whether added during differentiation or during maturation.

BARTHOLOME et al. utilize as a reference the "classical" protocol for differentiating monocytes in the presence of IL-4 and GM-CSF. As a result, Applicants respectfully disagree as to the contention that IL-4 could be considered as a maturation agent. Indeed, in view BARTHOLOME et al., IL-4 cannot be used as a maturation agent since the cells obtained in the presence of GM-CSF and IL-4 are immature (BARTHOLOME et al., page 472 and 473).

Thus, BARTHOLOME et al. observe that dendritic cells differentiated in the presence of IFN-beta, induce less IFN-gamma secretion by alloreactive T cells (Table 3, page 476). This stands in contrast with data from the present application (Figure 6C, Figure 9C, Figure 10B). Dendritic cells are obtained within 3 days with IFN and GM-CSF and induce higher synthesis of IFN-gamma by T-cells than dendritic cells obtained in the presence of IL-4 and GM-CSF, both in alloreactive reactions and in a primary response.

Thus, BARTHOLOME et al. do not disclose or suggest a process for obtaining dendritic cells within 3 days from

mononuclear cells in culture, wherein said mononuclear cells are put in contact, from the beginning of the culture with type I interferon at a final concentration greater than 400 IU/ml and in the absence of IL-4, as does the claimed invention.

Claims 1-25 were rejected under 35 USC 102(b) as allegedly being anticipated by PAQUETTE et al. This rejection is respectfully traversed.

PAQUETTE et al. is directed to the differentiation of blood monocytes in the presence of GM-CSF (500 U/ml) alone, or in combination with IL-4 (1000 U/ml), or with IFN-alpha-2b (from 200 to 5000 U/ml). Dendritic cells obtained present a dendritic cell morphology, with lobulated nuclei and fine cytoplasmic projections (page 359, right column). The immunophenotype of dendritic cells grown in IFN-alpha and GM-CSF consists of high levels of class I and II HLA proteins, CD80, CD86 and CD40 co-stimulatory proteins, and CD83 antigen expressed by a minority (about 17%) of the cells (Table 1). Dendritic cells obtained are antigen-presenting cells as seen in MLR reactions with alogenic T lymphocytes (Figure 8), are able to take up FITC-conjugated dextran (Figure 9), and to take up and present exogenous tetanus toxin to autologous T lymphocytes (Figure 10).

PAQUETTE et al. do not describe or suggest a process wherein type I IFN could mediate the differentiation of monocytes into differentiated dendritic cells as early as 3 days. In fact, it is generally thought that full differentiation takes from 5 to

APPENDIX:

The Appendix includes the following items:

- CELLA et al., "Ligation of CD40 on Dendritic Cells Triggers Production of High Levels of Interleukin-12 and Enhances T Cell Stimulatory Capacity: T-T Help via APC Activation"

- CELLA et al., "Maturation, Activation, and Protection of Dendritic Cells Induced by Double-stranded RNA"

7 days to occur, as it is true of conventional dendritic cells obtained with IL-4 and GM-CSF and for the cells described by PAQUETTE et al. The claimed invention, on the contrary, obtains active dendritic cells from monocytes within 3 days differentiation process.

As a conclusion, PAQUETTE et al. do not disclose or suggest a process for obtaining DENDRITIC CELLs within 3 days from mononuclear cells in culture, wherein said mononuclear cells are put in contact, from the beginning of the culture, with type I iinterferon at a final concentration greater than 400 IU/ml, as does the claimed invention.

Thus, in view of the present amendment and the foregoing remarks, applicants believe that this application is in condition for allowance with claims 54-71, as presented. Allowance and passage to issue on this basis are respectfully requested.

Charge the fee of $86 for the one independent claim added herewith to Deposit Account No. 25-0120.

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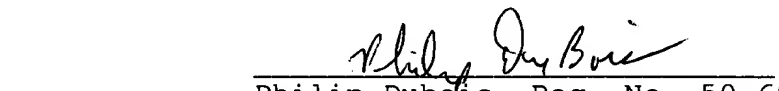
The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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